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| PRE-APPEAL BRIEF REQUEST FOR REVIEW | | Docket Number (Optional) <div style="text-align: center;">C1040.70006US00</div> | |
| | Application Number 09/316,199-Conf. #7506 | Filed May 21, 1999 | |
| | First Named Inventor Michael J. McCluskie et al. | | |
| | Art Unit 1633 | Examiner I. Popa | |
| <p>Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.</p> <p>This request is being filed with a notice of appeal.</p> <p>The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.</p> <p>I am the</p> <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 60%;"> <p><input type="checkbox"/> applicant /inventor.</p> <p><input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)</p> <p><input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>48,207</u></p> <p><input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____</p> </div> <div style="width: 35%; text-align: center;"> <p>_____ /Maria A. Trevisan/ Signature</p> <p>_____ Maria A. Trevisan Typed or printed name</p> <p>_____ 617.646.8000 Telephone number</p> <p>_____ August 21, 2012 Date</p> </div> </div> <p>NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.</p> | | | |
| <input type="checkbox"/> *Total of _____ forms are submitted. | | | |

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Dated: August 21, 2012

Electronic Signature for Nicole Millette Lapomardo: /Nicole Millette Lapomardo/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Michael J. McCluskie et al.
Application No.: 09/316,199
Confirmation No.: 7506
Filed: May 21, 1999
For: METHODS AND PRODUCTS FOR INDUCING MUCOSAL IMMUNITY
Examiner: I. Popa
Art Unit: 1633

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Dated: August 21, 2012

Electronic Signature for Nicole Millette Lapomardo: /Nicole Millette Lapomardo/

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Pursuant to United States Patent and Trademark Office OG Notices: 12 July 2005 - New Pre-Appeal Brief Conference Pilot Program, a request for a review by a panel of examiners (“the Panel”) of an identified matter on appeal is hereby co-submitted with a Notice of Appeal. The review is requested because the obviousness-type double patenting and obviousness rejections maintained in the final Office Action dated February 21, 2012 are improper due to legal and/or factual deficiencies. All rights to address additional matters on appeal in any subsequent appeal brief are hereby reserved.

REMARKS

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are pending and under examination in the instant application. The claimed invention provides methods for inducing a mucosal immune response in a subject in need of a mucosal immune response by administering an effective amount of a CpG oligonucleotide to a mucosal surface of the subject. The oligonucleotide may be co-administered together with an antigen to the same mucosal surface.

In the final Office Action dated February 21, 2012 (“FOA”), the Examiner rejected the claims under

(a) obviousness-type double patenting over (i) US 8202688 and (ii) US 7488490 in view of US 6689757, and

(b) 35 U.S.C. §103(a) over US 6239116 (Krieg et al.) in view of US 6426334 (Agarwal et al.), US 6042838 (Briles et al.), US 6689757 (Craig), and Kincy-Cain et al., *Infection and Immunity*, 1996, 64:1437-40.

Obviousness-type Double Patenting Rejections over US 8202688 and US 7488490

Instant claims 1, 5-9, 12, 15-18, 22, 129, 135-137 and 139-142 are rejected in view of claims 1, 4, 5, 9-11 and 13 of US 8202688 and instant claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are rejected in view of claims 1-22 of US 7488490 in view of US 6689757. US 8202688 is a continuation of US 7488490. The final Office Action states, with respect to both rejections, that “although the application claims do not recite a mucosal immune response, such is inherent to the application method.” (Pages 4 and 6, FOA; Applicant assumes the “application” is the cited patent). The Examiner further relies on passages in the specification of the cited patents that provide examples of administration routes including mucosal and non-mucosal (e.g., transdermal and parenteral) administration routes. Based on those passages, the Examiner concludes that mucosal immune responses are inherently induced when the claimed methods of the cited patents are practiced even though such claimed methods are not limited to mucosal administration.

Applicant considers the double-patenting rejections to be in error for at least two reasons.

First, the rejections are based on information provided only in the instant application and therefore involve impermissible hindsight. The instant application is the first disclosure of the

ability of CpG oligonucleotides to generate a mucosal immune response when administered to a mucosal site. This activity was unknown prior to the invention. The instant claims, which recite induction of a mucosal immune response in a subject in need of a mucosal immune response, would not have been obvious to one of ordinary skill in the art at the time of the invention based on the claims of the cited patents because it was not known, nor could it have been reasonably expected, prior to the invention that CpG oligonucleotides could induce mucosal immunity.

Second, the obviousness rejections are based on an inherency argument, and this too is impermissible. An obviousness rejection cannot be based on that which is unknown at the time of the invention. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993), MPEP 2141.02(V). As stated above, it was unknown that CpG oligonucleotides could induce mucosal immunity when administered to mucosal surfaces. Nothing in either of the cited patents teaches that a CpG oligonucleotide induces a mucosal immune response, and nothing in either patents teaches a subject that is in need of a mucosal immune response.

Moreover, the Examiner's conclusion that a mucosal immune response is inherent to the claimed methods of the cited patent methods is also factually and legally incorrect. The claimed methods of the cited patents recite administration of oligonucleotides generally. They are not limited to mucosal administration; rather administration may be via a mucosal route or it may be via a non-mucosal route, based on the non-limiting specification passages cited by the Examiner. Practice of the claimed method therefore does not necessarily require mucosal administration and it does not necessarily result in induction of a mucosal immune response. If a feature is simply possible, but not necessary, it is not inherent. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.); MPEP 2112(IV).

In the absence of hindsight and inherency, there is no teaching of various limitations of the rejected claims, and accordingly the claims as a whole would not be obvious to one of ordinary skill. For at least these reasons, Applicant respectfully submits that the instant claims are not obvious variants of the claims of US 8202688 and US 7488490.

Rejection under 35 U.S.C. § 103(a)

Instant claims 1, 5-9, 12, 15-18, 22, 129, 135-137 and 139-142 are rejected under 35 U.S.C. § 103(a) in view five references: US 6239116 (Krieg et al.) in view of each US 6426334 (Agarwal et al.), US 6042838 (Briles et al.), US 6689757 (Craig) and Kincy-Cain et al., *Infection and Immunity*, 1996, 64:1437-40.

The obviousness rejection under 35 U.S.C. 103(a), like the obviousness-type double patenting rejections, is improperly premised on hindsight and inherency. (Pages 8-9, FOA, “The limitation of inducing a mucosal immune response is inherent to the method of Krieg et al. because all that is required to achieve such is to administer their oligonucleotide to a mucosal site.” and “The limitation of the intranasal immunization resulting in mucosal immunity at remote sites ... is an inherent feature of their method because all that is required to achieve such is to intranasally administer their oligonucleotide.”)

As stated above, an obviousness rejection cannot be based on that which is unknown at the time of the invention. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993), MPEP 2141.02(V). Prior to the invention, it was unknown that CpG oligonucleotides could induce mucosal immunity when administered to mucosal surfaces. The cited references do not teach, inter alia, that CpG oligonucleotides induce mucosal immune responses (claims 1, 136, 137, 138, 139, 141, and claims dependent thereon), that CpG oligonucleotides should be administered to subjects in need of a mucosal immune response (claims 1, 136, 137, 138, 139, 141, and claims dependent thereon), or that administration of a CpG oligonucleotide at one mucosal site induces a mucosal immune response at a remote mucosal site (claim 26). The Examiner relies on inherency to evidence each of these claim limitations. Even if, for the sake of argument, such limitations were inherent, then they would not be recognized by or known to one of ordinary skill, and they could not be obvious to one of ordinary skill.

The Examiner additionally argues that induction of mucosal immune responses by administration of CpG oligonucleotides was known or was reasonably expected prior to the invention because, according to the Examiner, Krieg et al. teaches that CpG oligonucleotides are capable of inducing IL-12 and Kincy-Cain et al. teaches that IL-12 induces mucosal immune responses. The latter statement is factually incorrect: Kincy-Cain et al. states that IL-12 can *augment* a mucosal immune response *that arises after* administration of intracellular pathogen S.

dublin. Induction and augmentation of an immune response are different. There is no teaching in Kincy-Cain et al. that IL-12 *induces* a mucosal immune response. The former statement, even if true, does not lead one of ordinary skill to conclude that CpG oligonucleotides induce mucosal immune responses because induction of IL-12 is not synonymous with induction of a mucosal immune response. Applicant has provided the Examiner with multiple references to establish this latter point (see Office Action Responses dated July 22, 2009 and April 9, 2010). However, the Examiner has chosen to disregard the totality of those teachings in favor of those of Kincy-Cain et al. This too is improper. MPEP 2143.01 (II).

The Examiner additionally argues that induction of mucosal immunity following oral administration of an antigen, as reported by Bergmann et al., Rev. Infect. Dis., 1988, 10:939-950), would lead one of ordinary skill in the art to conclude that Krieg et al. teach inducing a mucosal immune response. Applicant has provided the Examiner with several references to establish that route of administration of an antigen does not dictate the immune response. (See Office Action Response dated April 9, 2010.) The Examiner has chosen to disregard the totality of those teachings in favor of those of Bergmann et al., and this is improper. MPEP 2143.01 (II).

In the absence of hindsight and inherency, and when the teachings of the references of record are taken into consideration in their entirety, there is no evidence that one of ordinary skill in the art would have known or reasonably expected that CpG oligonucleotides were capable of inducing a mucosal immune response. A prima facie case of obviousness has not been made. For at least these reasons, Applicant respectfully submits that the instant claims are not rendered obvious by the cited references.

CONCLUSION

For the reasons set forth above, Applicant believes that the instant application is in condition for allowance. Issuance of a Notice of Allowance is therefore respectfully requested.

If this document is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed fee, please charge any deficiency to Deposit Account No. 23/2825 under Docket No. C1040.70006US00 from which the undersigned is authorized to draw.

Application No. 09/316,199
Confirmation No. 7506

- 6 -

Docket No.: C1040.70006US00

Respectfully submitted,

Dated: August 21, 2012
x08.21.12

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Electronic Patent Application Fee Transmittal

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|--|--|-----------------|---------------|-----------------------------|
| Application Number: | 09316199 | | | |
| Filing Date: | 21-May-1999 | | | |
| Title of Invention: | METHODS AND PRODUCTS FOR INDUCING MUCOSAL IMMUNITY | | | |
| First Named Inventor/Applicant Name: | Michael J McCluskie | | | |
| Filer: | Maria A. Trevisan/Nicole Millette Lapomardo | | | |
| Attorney Docket Number: | C1040/7006HC | | | |
| Filed as Large Entity | | | | |
| Utility under 35 USC 111(a) Filing Fees | | | | |
| Description | Fee Code | Quantity | Amount | Sub-Total in USD(\$) |
| Basic Filing: | | | | |
| Pages: | | | | |
| Claims: | | | | |
| Miscellaneous-Filing: | | | | |
| Petition: | | | | |
| Patent-Appeals-and-Interference: | | | | |
| Notice of appeal | 1401 | 1 | 620 | 620 |
| Post-Allowance-and-Post-Issuance: | | | | |
| Extension-of-Time: | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD(\$) |
|------------------------------------|----------|----------|--------|----------------------|
| Extension - 3 months with \$0 paid | 1253 | 1 | 1270 | 1270 |
| Miscellaneous: | | | | |
| Total in USD (\$) | | | | 1890 |

Electronic Acknowledgement Receipt

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| EFS ID: | 13551413 |
| Application Number: | 09316199 |
| International Application Number: | |
| Confirmation Number: | 7506 |
| Title of Invention: | METHODS AND PRODUCTS FOR INDUCING MUCOSAL IMMUNITY |
| First Named Inventor/Applicant Name: | Michael J McCluskie |
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| Filer: | Maria A. Trevisan/Nicole Millette Lapomardo |
| Filer Authorized By: | Maria A. Trevisan |
| Attorney Docket Number: | C1040/7006HC |
| Receipt Date: | 21-AUG-2012 |
| Filing Date: | 21-MAY-1999 |
| Time Stamp: | 22:07:33 |
| Application Type: | Utility under 35 USC 111(a) |

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| Submitted with Payment | yes |
| Payment Type | Credit Card |
| Payment was successfully received in RAM | \$ 1890 |

| RAM confirmation Number | | 6942 | | | |
|---|-------------------------------|----------------------------------|--|------------------|------------------|
| Deposit Account | | 232825 | | | |
| Authorized User | | TREVISAN,MARIA A. | | | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges) | | | | | |
| File Listing: | | | | | |
| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
| 1 | Miscellaneous Incoming Letter | C104070006US00-TRN-MAT.pdf | 27731 | no | 1 |
| | | | 84f3b21f4a730a1299db69dae63c6c5b40399389 | | |
| Warnings: | | | | | |
| Information: | | | | | |
| 2 | Fee Worksheet (SB06) | C104070006US00-FEE-MAT.pdf | 33080 | no | 1 |
| | | | 67c3f4cc7dff793480a985ee2632eb41aac89560 | | |
| Warnings: | | | | | |
| Information: | | | | | |
| 3 | Extension of Time | C104070006US00-EXT-MAT.pdf | 23216 | no | 1 |
| | | | 88e3160d09e48f9f1ee664affb607b003f66da2a | | |
| Warnings: | | | | | |
| Information: | | | | | |
| 4 | Notice of Appeal Filed | C104070006US00-NAPL-MAT. pdf | 21972 | no | 1 |
| | | | 3ed6d46557c6fcd3053e02ca684da8d1cf05bccf | | |
| Warnings: | | | | | |
| Information: | | | | | |
| 5 | Pre-Brief Conference request | C104070006US00-PAPB1-MAT. pdf | 20794 | no | 1 |
| | | | 30553f0c580970d4727141dff11c06f86968b258 | | |
| Warnings: | | | | | |
| Information: | | | | | |
| 6 | Pre-Brief Conference request | C104070006US00-PAPB2-MAT. pdf | 45330 | no | 6 |
| | | | 57ff5f8190d3ab5806d33f2e66ae20b91ff7ca20 | | |
| Warnings: | | | | | |
| Information: | | | | | |
| 7 | Fee Worksheet (SB06) | fee-info.pdf | 32446 | no | 2 |
| | | | 9e06dd14e0bb503adb970482e5b39905493940e9 | | |
| Warnings: | | | | | |
| Information: | | | | | |
| Total Files Size (in bytes): | | | 204569 | | |

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

| | | |
|---|------------------------|------------------------|
| <h1 style="margin: 0;">TRANSMITTAL FORM</h1> <p style="margin: 10px 0 0 0;"><i>(to be used for all correspondence after initial filing)</i></p> | Application Number | 09/316,199-Conf. #7506 |
| | Filing Date | May 21, 1999 |
| | First Named Inventor | Michael J. McCluskie |
| | Art Unit | 1633 |
| | Examiner Name | I. Popa |
| Total Number of Pages in This Submission | Attorney Docket Number | C1040.70006US00 |

| ENCLOSURES <i>(Check all that apply)</i> | | |
|---|--|---|
| <input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR 1.52 or 1.53 | <input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD | <input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input checked="" type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Form PTO/SB/33 (Pre-Appeal Brief Request for Review); Pre-Appeal Brief Request for Review (6 pg.) |
| <div style="border: 1px solid black; width: 150px; float: left; margin-right: 10px; padding: 2px;">Remarks</div> | | |

| SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT | | | |
|--|--------------------------------|----------|--------|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /Maria A. Trevisan/ | | |
| Printed name | Maria A. Trevisan | | |
| Date | August 21, 2012 | Reg. No. | 48,207 |

x08.21.12

| Certificate of Electronic Filing Under 37 CFR 1.8 | |
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| Dated: August 21, 2012 | Electronic Signature for Nicole Millette Lapomardo: /Nicole Millette Lapomardo/ |